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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/585,645	06/01/2000	Hudà Y. Zoghbi	P01899US2	4965

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EXAMINER
QIAN, CELINE X

ART UNIT	PAPER NUMBER
1636	16

DATE MAILED: 06/03/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/585,645	ZOGHBI ET AL.	
	Examiner	Art Unit	
	Celine Qian	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 March 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-50 and 112-123* is/are pending in the application.

4a) Of the above claim(s) *49,120 and 122* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-48,50,112-119,121 and 123* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 40-50, 112-123 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 15 is acknowledged. The traversal is on the ground(s) that there is no search burden to examine Group I and III together. This is not found persuasive because the inventions are patentably distinct for reasons on the record set forth in the Office Action mailed on 1/15/02. A search of the subject matter of one invention would not be co-extensive with a search of the other invention, and therefore the search would be burdensome. Moreover, each invention is capable of supporting a separate patent.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 49, 120 and 122 are withdrawn from consideration for being directed to non-elected subject matter. Claims 40-48, 50, 112-119, 121 and 123 are currently under examination.

Drawings

The drawings are objected to because of the informalities as indicated by Draftsperson on PTO form 948 (see attached form). A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance. Any response to this office action which does not response to the above objections will be considered non-responsive.

Specification

The disclosure is objected to because of the following informalities: this application contains sequence disclosure that fails to comply with the requirements of 37 CFR 1.821 through 1.825. The amino acid sequence on page 33 line 22 lacks sequence identifier. On page 51 line 8, the actual number after "SEQ ID NO" is missing. Appropriate correction is required.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (on page 28, line 11). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

Claims 40-48, 50, 112-119, 121 and 123 are objected to for containing non-elected subject matter. For example, claim 40 contains the limitation that an amino acid is delivered to a cell, however, Applicant has elected group I, in which a nucleic acid is delivered to the cell. Amending the claims such that they are only directed to elected inventions is required.

Claim 45 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The recitation of "nucleic acid" in claim 45 does not further limit the parent claim 44. Appropriate correction is required.

Claim 121 is objected to for being dependent on a non-elected claim (120). Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40-48, 50, 112-119, 121 and 123 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a method of generating hair cells comprising delivering a therapeutically amount of an atonal-associated nucleic acid sequence to a cell in an animal. The specification discloses that "atonal-associated nucleic acid" comprises any nucleic acid sequence which is the Drosophila atonal nucleic acid sequence or is any sequence homologous to said sequence. The specification defines the atonal-associated sequence include any sequence that share 25% homology with the Drosophila atonal nucleic acid sequence (see page 23, lines 9-18). However, the specification only discloses that Math1 knockout mouse lacks inner hair cells development. The specification fails to demonstrate any other "atonal associated" nucleic acid sequences that share greater than 25% homology with Math1 have the same function. The prior art does not teach any atonal associated nucleic acid having the same disclosed function as Math1. In addition, the specification fails to disclose a functional region of Math1 that is responsible for hair cell generation. The state of art teaches sequence identity alone is insufficient to accurately predict the function of a protein (see Bork, Genome Research, 10:348-400, 2000). Therefore, as "atonal associated nucleic acid" and "nucleic acid sequence encodes a

polypeptide which has at least 80% identity to about 20 contiguous amino acid residues of SEQ ID NO: 58" constitute a vast genus of DNAs, the structural elements that the nucleic acid must share to have the disclosed hair cell generating function is missing. As such, the invention is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 40-48, 50, 112-119, 121 and 123 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The nature of the invention is a method of generating hair cells comprising delivering a therapeutically effective amount of an atonal associated nucleic acid sequence to a cell of an animal. The specification disclose that homozygous disruption of Math1, a mouse ortholog of Drosophila atonal gene, results in loss of hair cell in inner ear (see page 78-79, example 5). The specification further discloses that the expression pattern of Math1 is similar to that atonal expression in Drosophila, and Math1 is expressed in Merkel cells (see page 86, example 11).

The state of art at the time of filing is silent for generating hair cells in an animal by administering a therapeutically effective amount of atonal associated nucleic acid to an animal. Generating hair cells in an animal is a complex issue because there are different types of hair cells (for example, inner ear hair cells, skin hair cells, and nostril hair cells etc) regulated by different signal transduction pathways within a particular type of animal, and further complicated by the fact that different species of animal have different hair and/or feather growing pattern (i.e.,

birds, non-human primate, and reptiles). In a most recent review of molecular mechanism regulating hair follicle development, Millar lists genes that involve in hair cell (skin) morphogenesis and differentiation (see figure 3, Molecular Mechanisms Regulating Hair Follicle Development, 2002, J. Invest. Dermatol., Vol 118: 216-225). Zine et al. (2001, The Journal of Neuroscience, Vol 21, No. 13: 4712-4720) teach that Hes1 and Hes5 activities are required for the normal development of the inner ear hair cells. Taken together with the data disclosed by the specification, it is clear that the genes involved in different types of hair cell development and differentiation are not the same. Therefore, whether Math1 can generate hair cells in any part of the body of an animal is unpredictable. In addition, it appears that the normal development of inner ear hair cells involve concerted activity of both Math1 and Hes1 and Hes5 genes. As such, generating inner ear hair cell in an animal simply by delivering nucleic acid encoding Math1 to said animal regardless the status of other hair regulatory genes such as Hes1 and Hes 5 is also unpredictable.

At the time of filing, the relevant art considered gene therapy as a whole to be unpredictable as modes of delivery that would provide efficient delivery and expression of genes encoding the protein in the target cells had not been developed. Clinical efficacy has not been achieved in any gene therapy protocol to date (see Verma et al., Gene Therapy Promises, problems and Prospects, Nature, Vol. 389, pg. 239, col. 1). Robbins et al., (1998) also indicated the problems associated with adenoviral delivery system including immune elimination of infected cells which often limits gene expression in vivo (See abstract, page 35). Mountain (2000) discusses gene expression system used in gene therapy and points out that each gene transfer system has its own combination of advantages and limitations (See Gene Therapy: the

first decade, col. 5, pg. 121). Therefore, whether a therapeutically effective amount of atonal associated nucleic acid can be delivered to anywhere within an animal and result in hair cell generation is unpredictable.

The specification discloses that "atonal-associated nucleic acid" comprises any nucleic acid sequence which is the Drosophila atonal nucleic acid sequence or is any sequence homologous to said sequence. The specification defines the atonal-associated sequence include any sequence that share 25% homology with the Drosophila atonal nucleic acid sequence (see page 23, lines 9-18). The specification only discloses that Math1 knockout mouse lacks inner hair cells development. The prior art does not teach any atonal associated nucleic acid as defined by the specification that have the same disclosed function as Math1. Absent teaching from the art, one skilled in the art would have to turn to specification for guidance. However, the specification fails to demonstrate any other "atonal associated" nucleic acid sequences that share greater than 25% homology with Math1 have the same function. Therefore, whether any nucleic acid having 25% or greater homology with Drosophila atonal gene can generate hair cell in an animal is unpredictable.

The breath of the claims is very broad. The broadest claim encompass a method of generating any type of hair cell in any kind of animal by delivery a therapeutic effective amount of any nucleic acid sharing 25% homology with atonal gene. The teaching of the specification is rather limited. The specification only teaches that Math1, an ortholog of atonal gene, is responsible for inner ear hair cell development in mouse. Absent teaching from prior art and guidance from specification, one skilled in the art would have to engage in undue amount of experimentation to overcome the problems discussed above to practice the method as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 40-48, 50, 114, 116 and 117 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 40-48 and 50, the word "said" renders the claims indefinite it is unclear which animal Applicants are referring to.

Regarding claim 114, the recitation "a liposome, a protein, a lipid, a carbonhydrate" renders the claim indefinite because neither of those is a vector.

Regarding claims 116 and 117, the term "operatively linked" renders the claims indefinite because it is unclear how to link two coding sequence operatively. A more clear and concise description is required.

Regarding claim 117, the term "protein transduction domain" renders the claim indefinite because it is unclear which part of the protein Applicants are referring to.

Claims 40-48 and 50 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: thereby hair cell develops in said animal.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celine X Qian whose telephone number is 703-306-0283. The examiner can normally be reached on 9:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Celine Qian, Ph.D.
June 3, 2002

REMY YUCEL, PH.D
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